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Date  
22-10-2008

Reference FR014EP	Application No./Patent No. 04758064.2 - 1222 / 1604014
Applicant/Inventor DANA-FARBER CANCER INSTITUTE, INC.	

**Summons to attend oral proceedings pursuant to Rule 115(1) EPC**

You are hereby summoned to attend oral proceedings arranged in connection with the above-mentioned European patent application.

The matters to be discussed are set out in the communication accompanying this summons (EPO Form 2905).

The oral proceedings, which will not be public, will take place before the Examining Division.

on 20.03.09 at 09.30 hrs. EPO Rijswijk  
Patentaan 2, NL-2288 EE Rijswijk (ZH)

No changes to the date of the oral proceedings can be made, except on serious grounds (see OJ EPO 10/2000, 456).

If you do not appear as summoned, the oral proceedings may continue without you (R. 115(2) EPC).

Your attention is drawn to Rule 4 EPC, regarding the language of the oral proceedings, and to the OJ EPO 9/1991, 489, concerning the filing of authorisations for company employees and lawyers acting as representatives before the EPO.

The final date for making written submissions and/or amendments (R. 116 EPC), is 20.02.09.

The actual room number as well as the waiting room numbers will be given to you by the porter in the foyer at the above EPO address.

Parking is available free of charge in the underground car park (see map enclosed).

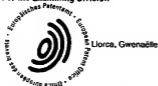
1st Examiner:  
Aguilera Merlo M

2nd Member:  
Brume A

Chairman:  
Botz J

For the Examining Division

Annexes:  
Confirmation of receipt (Form 2936)  
Communication (EPO Form 2906)  
DB



Registered letter with advice of delivery  
EPO Form 2008 12.07 (J01AL03-A020) 15.10.08

to EPO postal service: 15.10.08

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The examination is being carried out on the following application documents:

**Description, Pages**

1, 3-6, 9-28, 30-126 as published  
2, 7, 29 filed with entry into the regional phase before the EPO

**Claims, Numbers**

1-33 filed with entry into the regional phase before the EPO

**Drawings, Sheets**

1/13-13/13 filed with entry into the regional phase before the EPO

- 1 Oral proceedings will be held according to Article 116 EPC.
- 2 Reference is made to the official communications of 12.06.2008 (C1), 07.10.2008 (C2; minutes of telephone conversation) and applicant's letter of reply dated 17.09.2008 (L1).
- 3 The following points will be subject of discussion during the proceedings.
- 4 The following documents (D) have been referred to during examination; the numbering is adhered to in the rest of the procedure:

- D1: BENDRE MANALI S ET AL: "Expression of interleukin 8 and not parathyroid hormone-related protein by human breast cancer cells correlates with bone metastasis in vivo." CANCER RESEARCH 1 OCT 2002, vol. 62, no. 19, 1 October 2002 (2002-10-01), pages 5571-5579, XP002468923 ISSN: 0008-5472
- D2: FREUND ARIANE ET AL: "IL-8 expression and its possible relationship with estrogen-receptor-negative status of breast cancer cells." ONCOGENE 16 JAN 2003, vol. 22, no. 2, 16 January 2003 (2003-01-16), pages 256-265, XP002468924 ISSN: 0950-9232
- D3: SALCEDO ROSALBA ET AL: "Combined administration of antibodies to human Interleukin 8 and epidermal growth factor receptor results in increased antimetastatic effects on human breast carcinoma xenografts" CLINICAL CANCER RESEARCH, THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, US, vol. 8, no. 8, August 2002 (2002-08), pages 2655-2665, XP002451870 ISSN: 1078-0432

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- D4: DE LARCO J E ET AL: "A potential role for interleukin-8 in the metastatic phenotype of breast carcinoma cells." THE AMERICAN JOURNAL OF PATHOLOGY FEB 2001, vol. 158, no. 2, February 2001 (2001-02), pages 639-646, XP002468925 ISSN: 0002-9440
- D5: GREEN A R ET AL: "Expression of cytokine messenger RNA in normal and neoplastic human breast tissue: identification of interleukin-8 as a potential regulatory factor in breast tumours." INTERNATIONAL JOURNAL OF CANCER. JOURNAL INTERNATIONAL DU CANCER 17 SEP 1997, vol. 72, no. 6, 17 September 1997 (1997-09-17), pages 937-941, XP002468927 ISSN: 0020-7136
- D6: WHITTAKER J L ET AL: "Differential expression of cellular oncogenes in benign and malignant human breast tissue." INTERNATIONAL JOURNAL OF CANCER. JOURNAL INTERNATIONAL DU CANCER 15 NOV 1986, vol. 38, no. 5, 15 November 1986 (1986-11-15), pages 651-655, XP002468929 ISSN: 0020-7136
- D7: PELLEGRINO M B ET AL: "Differential expression of keratins 13 and 16 in normal epithelium, benign lesions, and ductal carcinomas of the human breast determined by the monoclonal antibody Ks8.12." CANCER RESEARCH 15 OCT 1988, vol. 48, no. 20, 15 October 1988 (1988-10-15), pages 5831-5838, XP002468930 ISSN: 0008-5472
- D8: CHEN ET AL: "A possible tumor suppressor role of the KLF5 transcription factor in human breast cancer." ONCOGENE, vol. 21, 2002, pages 6567-6572,

**5 CLARITY, SUPPORT AND DISCLOSURE (Arts. 84 and 83 EPC)**

- 5.1 Applicant did not reply in L1 to the objections raised in C1 (Item 2) for lack of clarity, support and disclosure (Arts. 84 and 83 EPC) with neither reasons nor amendments.

Hence, the objections are maintained and the applicant is invited to consider amendments and/or reasons in preparation for the oral proceedings.

For convenience, the objections are repeated below (items 5.2 to 5.5).

- 5.2 Present claims 2, 24, 26 and 27 relate to an extremely large number of possible

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methods and products; virtually, any diagnostic method, array, kit of probes or kit of antibodies for the detection of any combination of 10, 11, 12... etc. out of the 1964 different gene markers listed in Tables 1-16. The number of possible combinations is so high that a lack of clarity and conciseness arises within the meaning of Article 84 EPC to such an extent as to render a meaningful examination over the whole of the claimed scope impossible.

In addition, it is noted that no particular combination of genes is explicitly selected as a preferred embodiment, and that none of the examples shows in practice any such particular combination. Hence, an opinion of patentability of said embodiments is currently not possible.

- 5.3 Present claims 15-19 relate to the use of products defined by reference to a desirable characteristic or property, namely their ability to inhibit the expression of a gene, or the binding of a protein to its ligand. The claims refer to all products having this characteristic or property, whereas the application provides support within the meaning of Article 84 EPC and disclosure within the meaning of Article 83 EPC for only a very limited number of such products, namely the antisense compounds mentioned in claim 19. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful examination over the whole scope of claims 15-19 is impossible.
- 5.4 Furthermore, claims 15-19 also lack clarity (Article 84 EPC). An attempt is made to define the products by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful examination over the whole of the claimed scope impossible.
- 5.5 The present request contains 19 (I) separate independent claims. Under Article 84 in combination with Rule 43(2) EPC an application may contain more than one independent claim in a particular category only if the subject matter claimed falls within one or more of the exceptional situations set out in paragraphs (a), (b) or (c) of Rule 43(2) EPC. However, none of them seems to apply in the present case.

## 6 UNITY OF INVENTION (Art. 82 EPC)

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- 6.1 The lack of unity objection raised in C1 (item 3) was contested by applicant in L1 and during the telephone conversation reported in C2. However, no agreement was reached and the Examining Division (ED) maintains the objection as formulated in C1. The paragraphs below repeat the objection for convenience (6.2 to 6.5) and summarize applicants argumentation and the reply by the ED (items 6.6 to 6.8).
- 6.2 The common concept of the application, as defined by the present claims, can be considered the provision of methods and products for diagnosis of breast cancer based on the detection of alterations in gene expression levels. However, this concept was well known at the date of priority: a quick MEDLINE search reveals more than 750 documents published before the priority date disclosing differential expression studies of breast cancer. Most of them would be sufficient to anticipate the present common concept. For example, D6, published 16 years before priority, discloses an expression profiling study of several oncogenes in breast cancer patients vs. controls.
- 6.3 In view of this prior art, and due to the fact that the disclosed methods and products as such are conventional in the field of genetic diagnosis/prognosis, the technical problem to be solved by the present invention can be considered as the provision of further expression markers which can be used in diagnosis/prognosis of breast cancer.

The solutions given by the present application, as defined by the present claims, are the 1964 genes listed in Tables 1-16. Each one of them represents an alternative solution to the technical problem posed.

Because no other technical features can be distinguished which, in view of the prior art could be regarded as special technical features in the sense of Rule 44 PCT, there is no single inventive concept underlying all these solutions in the sense of rule Article 82 EPC.

- 6.4 Consequently, there is a lack of unity, and the methods and products claimed based on each one of the expression markers claimed are different inventions not belonging to a common inventive concept. The number of non-unitary inventions is thus 1964:

**Invention 1:** Methods for diagnosis, prognosis or staging of breast cancer based on determining the level of expression of interleukin 8. Products to carry out said methods. Claims 1, 3-14, 19-23, 30-33 (all partially).

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**inventions 2-1964:** Methods for diagnosis, prognosis or staging of breast cancer based on determining the level of expression of HIN-1. Products to carry out said methods. Claims 1, 3-14, 19-23, 30-33 (all partially).

[idem. for each one of the remaining 1962 different genes listed in Tables 1-16]

- 6.5 In compliance with Rule 164(1) EPC, the Search Division defined invention 1 as directed to the first of the 1964 solutions mentioned in the claims, namely the first gene of Table 1 mentioned in claim 1, and issued a Supplementary Search Report covering said invention as defined above.

The ED agrees with this decision of the Search Division.

- 6.6 Applicant argues in L1 that there is a clear unifying feature among all the genes referred to in claim 1 (i.e. the genes of Table 1), namely that they are all expressed at lower level in cancer cells vs. control cells. This feature is allegedly not present in any of the prior art documents cited.

- 6.7 The ED disagrees in two points:

- 6.7.1 First, the definition of the common concept of the application and the evaluation of *special* technical features must be carried out in the light of the whole application, as defined by the present claims, not only by claim 1. The Guidelines are clear in this respect: "The expression "special technical features" means, in any one claim, the particular technical feature or features that define a contribution that the claimed invention **considered as a whole** makes over the prior art" (Guidelines CIII, 7.2; emphasis added).

Indeed, the feature of "lower level" is not shared by all the claims; for instance, independent claims 3, 4 cover all types of alteration in expression levels, while independent claims 5, 7 and 9 are directed to markers with *higher* expression levels in cancer cells. Hence, the "lower level" cannot be considered a technical feature of the present application considered as a whole.

- 6.7.2 Second, the feature of "lower level" does not make a novel and inventive contribution to the art in the sense of Rule 44(1) EPC. In the hypothetical case

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that the subject-matter of the application were restricted to claim 1 (e.g. by deletion of claims 2-33) the feature of "lower level" would be shared by all expression markers of Table 1.

However, this feature is obviously not new. The numerous expression profiling studies of breast cancer published before priority date comprise many over- and under-regulated expression markers; in particular, many tumor suppressor genes are under-expressed in cancer cells. This is considered common knowledge to the skilled person but, for the sake of completeness, an example of this is introduced here: D8 discloses "lower" expression levels of KLF5 as a marker of breast cancer (see Abstract).

Moreover, the ED division fails to see how the mere choice of "lower" between the two possibilities of altered expression levels, namely *higher* and *lower*, could be considered an inventive contribution to the art. In fact, this choice appears to be a standard way of grouping and roughly classifying the results of expression profiling experiments.

It must be noted that the genes of Table 1 do not share any other feature than being genes with lower expression levels in cancer cells. Thus, contrary to applicant's statements in L1, it is not necessary that the prior art cited in this hypothetical case would comprise one of the genes of Table 1. Every document disclosing reduced gene expression levels in cancer vs. control cells would be sufficient to anticipate this hypothetical common concept.

- 6.8 Applicant contends that, in case of lack of unity, invention 1 should be defined by claim 1 completely, but failed to provide a valid analysis of *special* technical features in the sense of Rule 44(1) EPC.

In this context, the applicant is also referred to Rule 44(2) EPC, which specifies that the determination whether a group of inventions forms or not a single general inventive concept shall be made without regard to whether the inventions are claimed in separate claims or as alternatives in a single claim, as in the present case, where the first of these alternatives is the first gene in Table 1.

- 6.9 With regard to the remaining questions raised by applicant in L1, namely the logic under the separation of claims into non-unitary inventions, the exact scope of the search and the lack of an invitation to pay additional fees, the answers were provided

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in the telephone conversation of 07.10.2008 (see C3).

Should the applicant have further doubts, these will be clarified during the oral proceedings.

## 7 CONCLUSIONS

- 7.1 The above listed defects are such that no further examination of compliance with Article 52 EPC will be carried out at this stage.

The applicant is invited to file new claims which take account of the above objections in preparation for the oral proceedings.

At present, the only way to proceed with the present application appears to be: (1) to limit the application to IL-8 and excise from the claims all references to inventions 2-1964 (see Rule 164(2) EPC; Guidelines, C-III, 7.11; G 2/92; OJ 10/1993, 591); and (2), to file only one independent claim per category (Rule 43(2) EPC).

The subject-matter to be excised may be made the subject of one or more divisional applications.

- 7.2 Should the applicant be ready to do so, he is invited to elaborate, in preparation for the oral proceedings, the reasons and/or experimental evidence which will be required in order to overcome the prejudice set by documents D1-D5, all of them disclosing the association between *higher* levels of IL-8 and breast cancer. No inventive step will be acknowledged in the absence of convincing reasons and/or experimental evidence of the technical effect on which such claim(s) would be based.
- 7.3 Should the applicant choose to maintain the present request, a refusal under Article 97(2) EPC on the grounds specified above is to be expected at the end of the oral proceedings on the grounds of lack of clarity, support, disclosure and unity (Articles 84, 83 and 82 EPC).



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Boards of Appeal

Chambres de recours

Case Number: T 0412/06 - 3.3.02

**DECISION**  
of the Technical Board of Appeal 3.3.02  
of 12 October 2006

**Appellant:** Max-Planck-Gesellschaft zur Förderung der  
Wissenschaften e.V.  
Hofgartenstraße 8  
D-80539 München (DE)

**Representative:** Weiss, Wolfgang  
Weickmann & Weickmann  
Patentanwälte  
Postfach 86 08 20  
D-81635 München (DE)

**Decision under appeal:** Decision of the Examining Division of the  
European Patent Office posted 13 October 2005  
refusing European application No. 00951521.4  
pursuant to Article 97(1) EPC.

**Composition of the Board:**

**Chairman:** B. Oswald  
**Members:** J. Riolo  
J. Willems